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Policies for Biodefense Revisited: The Prioritized Vaccination Process for Smallpox

by

Moshe Kress

September 2003

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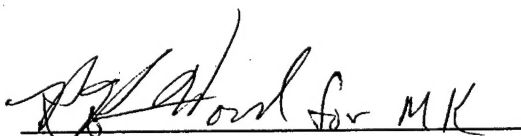**MONTEREY, CA 93943-5000**

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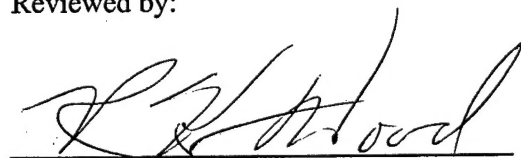Superintendent

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ABSTRACT

Handling bioterror events that involve contagious agents is a major concern in the war against terror, and is a cause for debate among policymakers about the best response policy. At the core of this debate stands the question which of the two post-event policies to adopt: *mass vaccination*—where maximum vaccination capacity is utilized to uniformly inoculate the entire population, or *trace* (also called *ring* or *targeted*) vaccination—where mass vaccination capabilities are traded off with tracing capabilities to selectively inoculate only contacts (or suspected contacts) of infective individuals. We present a dynamic epidemic-intervention model that expands previous models by capturing some additional key features of the situation and by generalizing some assumptions regarding the probability distributions of inter-temporal parameters. The model comprises a set of difference equations. The model is implemented to analyze alternative response policies. It is shown that a mixture of *mass* and *trace* vaccination policies—the *prioritized* vaccination policy—is more effective than either of the two aforementioned policies.

1. Introduction

Responding to a bioterror event that involves contagious agents has become a major issue in the war against terror. There are many operational and logistic decisions that must be made carefully in order to effectively cope with such a threat. These decisions are roughly divided into two levels: Structural (strategic) decisions that need to be made in advance, and operational (real-time) decisions that must be made during the event. Some of the structural (strategic) problems are:

- How many vaccines to produce and stock?
- Which supply management policies to apply for allocating, deploying, and controlling inventories of vaccines and other related supplies?
- What infrastructure (vaccination stations, quarantining facilities, etc.) is required?
- What vaccination procedure (e.g., inoculation only, pre-vaccination screening for contra indication) to adopt?
- How to determine the manpower requirements and personnel assignment?

The operational (real-time) decisions include:

- Identifying the type of the bioterror event.
- Managing the contact tracing process (if applied).
- Prioritizing efforts with respect to monitoring, isolating, quarantining, tracing, and vaccinating.
- Coordinating the supply chain of vaccines and other supplies.
- Identifying bottlenecks and potential congestion.
- Determining capacities and setting service rates.

One of the most critical decisions—a decision that has both structural and operational implications—is which vaccination policy to adopt. This question has generated debate among policymakers [1] and has also drawn much attention by the general public [2], [3]. The vaccination policy decision has two levels. At the first level, policymakers must choose between essentially two options: a preemptive approach in which the entire population is pre-vaccinated, and a "wait and see" approach where post-attack emergency

1

response (vaccination, quarantine, isolation) commences following an outbreak of the disease. Mixtures of these two options are possible too, i.e., pre-vaccination of first responders (e.g., health-care and law-enforcement personnel) only. Sociological and psychological considerations (is there a real threat or just a perceived one?) coupled with medical considerations (fear of side effects) have hindered policy makers from taking any significant preemptive action so far.

If no significant preemptive measures are taken, the question at the second level is which post-event vaccination policy to adopt. The two policies that have been examined so far are *mass* vaccination and *trace* vaccination. In mass vaccination, maximum vaccination capacity is utilized to uniformly inoculate the entire population. In *trace* (also called *ring* or *targeted*) vaccination, only limited vaccination capacity is utilized to selectively inoculate contacts (or suspected contacts) of infective individuals.

Several researchers have attempted to address the issue of the post-event vaccination process in the case of smallpox, and in particular to compare mass vaccination to trace vaccination. Kaplan, Craft, and Wein [4] propose a continuous-time deterministic model that comprises 17 ordinary differential equations. Their model, details of which are reported in [5], captures many important aspects of the situation, including the "race to trace." The race to trace reflects the time constraints on the effectiveness of the vaccination process due to the limited time period in which an infective is vaccine-sensitive or "immunable." They assume exponential distributions with regard to all of the time parameters (e.g., incubation time, infectious time) and therefore the transitions in their model are not dependent on the "age" of an individual in a certain stage of the epidemic. They also ignore the effect of the epidemic initial conditions. Some epidemic and operational parameters may have different values at the early stages of the epidemic than later on. For example, the vaccination process may need some setup time during which only a portion of the potential vaccination capacity can be utilized. Also, during the first generation of the disease (prior to detection) the infection rate may be higher and the isolation rate may be lower because of lack of situational awareness. Kaplan *et al.* [4] conclude that under reasonable conditions regarding the initial attack

2

size and the epidemic's spread parameters, mass vaccination is generally more effective than trace vaccination.

Contrary to the analytic macroscopic approach in [4], [5], Halloran, Longini, Azhar, and Yang [6] use a detailed simulation to model at the micro level a smallpox transmission process in a (socially) structured community of 2,000 people. The disease transmission process in their model takes into account the social structure of the community, attempting to better represent the way the epidemic spreads in the population. They assume that the random variables that are associated with the duration of the various stages of the epidemic are uniformly distributed—an assumption that can hardly be justified. They assert that according to their simulation, trace vaccination would prevent more smallpox cases per dose of vaccine than would mass vaccination. Due to the imbedded nonlinearities in the epidemic process, it is not clear if their conclusions derived for a population of 2,000 may also apply to a population of say 10 million. Their model also lacks the operational and logistical aspects that are accounted to in [4]. However, the Halloran *et al.* and the Kaplan *et al.* models are not inconsistent. The model in [4] gives similar results as the model in [6] when supplied the inputs used in [6] (see [7]).

A Markov chain model of the epidemic progression is utilized by Meltzer, Damon, LeDuc, and Millar [8] to analyze various response options. Their conclusion is that only a combination of vaccination with an effective quarantine may eradicate the epidemic. The paper contains some epidemic progression data—some of which is used in our paper. Koopman [9] reviews the studies the models in [4] and [6] and suggests a possible third modeling approach based on a network model that describes the links among individuals. Such models are reported in [10] and [11]. Other researchers ([12], [13]) use distance-based models to analyze ring vaccination, which is a geographically oriented version of trace vaccination. Spatial effects are also examined in [14], where a high-resolution computational model is developed. In a more recent publication [15], the authors develop a stochastic model of outcomes under various control policies. Their

3

model is limited in the sense that they assume, rather than derive, the post intervention basic reproductive rate.

There are two main objectives in the current research. The first objective is to develop a flexible, large-scale analytic model that expands and generalizes previous models. Our model is conceptually similar to the model in [4], but it differs in the use of discrete rather than continuous time. Thus, it is in the form of a set of difference equations rather than differential equations. As it will be shown later on, a discrete model can more easily capture certain key operational, logistical, and epidemiological aspects of the situation. Also, in contrast to the constant hazard functions (exponential distributions) of the time parameters in [4] and the uniform distributions of these parameters in [6], our model makes no assumptions with regard to these distributions. It can take any finite-support distributions—including empirical. The model also explicitly represents the age-dependent transitions among the various stages of the epidemic. We also distinguish between the initial conditions of the epidemic and its operational and logistical steady-state parameters.

The second objective is to propose an alternative vaccination policy, the *prioritized vaccination policy* (*PVP*), which may be viewed as a mixture of the *mass vaccination policy* (*MVP*) and the trace vaccination policy (*TVP*). We demonstrate that under a set of realistic assumptions regarding the epidemic parameters and the operational and logistical capabilities to handle it, the *PVP* is significantly more effective than either the *MVP* or the *TVP* individually.

The paper is organized as follows: in Section 2 we discuss the possible response options for a bioattack, and in Section 3 we present the model. The three vaccination policies—*PVP*, *MVP*, and *TVP*—are analyzed in Section 4. First, we examine the base case, which is similar to the scenario described in [4], and then we perform sensitivity analysis. Section 5 contains the summary and conclusions.

2. The Epidemic and the Possible Interventions

We consider a situation where a malevolent agent engages a population with an act of terror by releasing the smallpox virus in a public area. This act of terror is clandestine, and the authorities are not aware of the event until a certain number of symptomatic patients are reported and diagnosed as carrying the disease. Once the epidemic is detected and identified, a response is initiated, which involves isolation, quarantine, tracing contacts and vaccinating some or all of the population. The disease has an incubation period before an infected individual becomes symptomatic. During the incubation period the infected individuals are not infectious, and therefore the disease is not transmitted to others. The incubation period is divided into two periods of time: the *immunable* (also called *vaccine sensitive*) period and the *non-immunable* period. During the immunable period, vaccination is effective. It will eradicate the disease from an infective at that stage with high probability. During the non-immunable period, vaccination is not effective, and therefore the infective will eventually become ill. Once the incubation period is over, the infected individual becomes infectious. The infectious period lasts as long as the symptoms still persist. As in [4], the transmission of the disease is in the form of homogeneous mixing.

At any given time t, the population of non-vaccinated individuals is divided into the following six possible stages:

S: Susceptible to the disease;

A: Infected, not yet infectious (incubating), and immunable (vaccine sensitive);

B: Infected, not yet infectious (incubating), and **not** immunable;

I: Infected, infectious, and not yet isolated;

Q: Infected, infectious, and isolated,

R: Removed, recovered, and immune or dead.

The durations of the stages A, B, I, and Q are random variables with probability mass functions $P_A(j), P_B(j), P_I(j)$, and $P_Q(j)$, respectively. The parameter j indicates the

number of days—the time resolution of the model—an individual stays at a certain stage. Note that while $P_A(j), P_B(j)$, and $P_Q(j)$ are determined purely by epidemic characteristics, $P_I(j)$ is affected also by the response process and in particular, the effectiveness of the detection and quarantine efforts. Numerical values of the various probability mass functions that are selected for the base case in the analysis are taken from [8].

Once the epidemic is identified, detected infectious individuals (in stage I) are isolated (moved to stage Q) and the vaccination process commences. Two potential vaccination queues may be formed: the *general queue* and the *tracing queue*. The general queue comprises non-vaccinated individuals (in stages S, A, and B) who are not in the tracing queue. The tracing queue comprises all non-vaccinated contacts named by an *index case*. An index case is a newly detected infectious individual. Because of the additional effort that is required to trace contacts, the service rate at the tracing queue is lower than that at the general queue. The *tracing service reduction factor* is the ratio between the service rates at the general queue and tracing queue. We assume that a certain portion of the vaccination capacity is allocated to the tracing queue and the rest is applied to the general queue.

The set of contacts that are named by a certain index case is called the *index set*. Let E denote the set of index cases and let J_i denote the index set of $i \in E$. The index set J_i may comprise three possible disjoint subsets:

$J_i(1)$ – Infected individuals not yet vaccinated;

$J_i(2)$ – Non-infected (susceptible) individuals not yet named or vaccinated;

$J_i(3)$ – Individuals named and vaccinated earlier by another index or already vaccinated in the general queue.

For a given index i the target population of the tracing process is $J_i(1)$. Tracing individuals in $J_i(2)$ is somewhat wasteful since there is no race to trace. The susceptible

individuals in $J_i(2)$ can be vaccinated in the more efficient general queue. Tracing individuals in $J_i(3)$ is clearly a waste of tracing capacity. Thus,

$$J_i = J_i(1) \cup J_i(2) \cup J_i(3) \tag{1}$$

and the tracing queue is generated by $\bigcup_{i \in E} J_i$.

To properly represent the effective vaccination rate at the tracing queue we need to introduce three terms: (*index case*) *i-infective*, *newly named i-infective*, and *potentially traceable*. An *i-infective* is an individual that has been infected by index case i. For each infective the transmitter is uniquely defined. That is, an infective cannot be infected twice. Notice that an *i*-infective may be named by another non-transmitter index case j before being named by its transmitter i. An *i*-infective, not previously named by another index case, nor vaccinated, which is named by index case i is called *newly-named i-infective*. An *i*-infective, not yet traced or vaccinated, is said to be *potentially traceable* (*PT*) if its corresponding transmitter i has been detected and interviewed. Let P_i denote the set of *PT* *i*-infectives. Clearly, the sets $P_i, \ i \in E$ are disjoint. A newly named *i*-infective is *PT*, but a *PT* i-infective may not be newly named if the corresponding index case failed to name this contact. The state *PT* is transient, that is, an *i*-infective is *PT* only during the time period when i is interviewed. An *i*-infective that has not been named by its corresponding index i becomes non-*PT* once again in the next period. Thus, an *i*-infective may pass through three possible states: pre-*PT*, *PT*, and post-*PT*. By definition, an individual in the post-*PT* state will never become *PT* again. He may be traced however by a non-transmitter index case. Also, an *i*-infective in the pre-*PT* state may never become *PT* if named by a non-transmitter. As in [4], we assume that $\Box J_i \Box = M$ for all index case i. Also, since we assume homogeneous mixing, that is, all index cases are identical with respect to the transmission process, $\Box P_i \Box = N$ for all index cases $i \in E$. However, unlike M that stays constant throughout the epidemic (e.g., $M = 50$ in [4]), $N = N(t)$ changes over time as the epidemic progresses. As in [4], we assume that $M \geq N(t)$ for all t, that is, the size of the index set always exceeds the number

of *PT* infectives. Finally, let ω_0 denote the probability that a *PT* infective is (newly) named by the corresponding index.

Note that the total number of *PT* infectives at time t is $Q_1(t)N(t)$, where $Q_1(t)$ is the number of index cases that are detected and interviewed at time t. Similarly, $Q_1(t)M$ is the total number of names generated at time t by the index cases. We assume that M represents the net number of newly named contacts. Therefore, the index sets are disjoint.

Let $\omega(t)$ denote the fraction of the index set that contains newly named infectives.

$$\omega(t) = \omega_0 \frac{N(t)}{M}. \tag{2}$$

Since there are no reliable estimates for ω_0, we will first assign, in the base case, a reasonable value for this parameter, and then we will perform a full-scale sensitivity analysis in Section 4.

The definitions in (2) are used as a backdrop for the more generalized definitions in Section 3.

Note that *MVP* and *TVP* generate only one queue each—*general queue* in *MVP* and *tracing queue* in *TVP*. The vaccination process that is proposed in this paper—*PVP*, which is described in the next section—generates both queues.

Figure 2.1 depicts the epidemic stages and the transitions among them. The subscripts indicate the age of a certain stage. The terms A_j^-, A_j^0, A_j^+ denote cohorts at epidemic age j in the pre-*PT*, *PT*, and post-*PT* stages, respectively. Notice that in the absence of a corresponding index case, an individual may move from stage A^- to stage B without being potentially traceable at all (see e.g., edge $A_1^- \rightarrow B_2$). One of the main objectives is to trace, as fast as possible and as many as possible, individuals in stage A^0 (see the shaded oval shape in Figure 2.1).
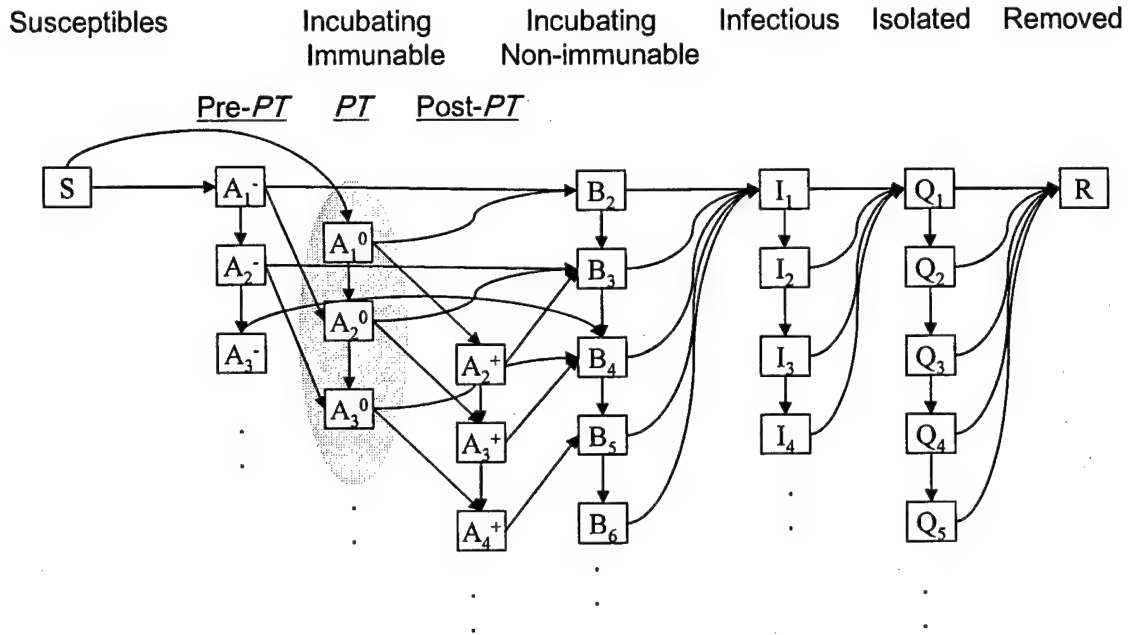
8

Figure 2.1: *The Epidemic Stages*

3. The Model

3.1 Notation

The various cohorts in the epidemic are:

$S(t)$ – Number of susceptibles at time t;

$A_j(t)$ – Number of *immunable* infectives in the j-th day of the incubation period,

$\quad\quad A_j(t) = A_j^-(t) + A_j^0(t) + A_j^+(t)$, where $A_j^-(t)$ are pre-PT, $A_j^0(t)$ are PT and $A_j^+(t)$ are post-PT;

$B_j(t)$ – Number of *non-immunable* infectives in the j-th day of the incubation period,

$\quad\quad B_j(t) = B_j^-(t) + B_j^0(t) + B_j^+(t)$, where $B_j^-(t)$ are pre-PT, $B_j^0(t)$ are PT and $B_j^+(t)$ are post-PT;

$I_j(t)$ – Number of infectious individuals in the j-th day of the infectious period;

$Q_j(t)$ – Number of isolated individuals in the j-th day of isolation.

Let,

$$A^-(t) = \sum_{j=1}^{\infty} A_j^-(t), \ A^0(t) = \sum_{j=1}^{\infty} A_j^0(t), \ A^+(t) = \sum_{j=1}^{\infty} A_j^+(t),$$

$$B^-(t) = \sum_{j=1}^{\infty} B_j^-(t), \ B^0(t) = \sum_{j=1}^{\infty} B_j^0(t), \ B^+(t) = \sum_{j=1}^{\infty} B_j^+(t), \qquad (3)$$

$$I(t) = \sum_{j=1}^{\infty} I_j(t).$$

Other parameters are:

$\alpha(t)$ – Infection rate;

$T(t)$ – The length of the tracing queue;

$L(t)$ – Total number of newly named infectives in the tracing queue;

$r_T(t)$ – Tracing rate;

$V(t)$ – Nominal vaccination/tracing capacity;

q – Proportion of the vaccination capacity allocated to the tracing queue;

$r_G(t)$ – Vaccination rate in the general queue;

$r^+(t)$ – The residual trace vaccination rate that is applied to individuals who are not newly named *PT* infectives (Recall that a *newly-named PT infective* is an infected individual that is named, for the first time, by the corresponding transmitter);

$\omega(t)$ – Estimated fraction of the tracing queue that contains newly named infectives;

ω_0 – The probability of naming a *PT* infective;

$w(t)$ – The rate at which non-*PT* infectives become *PT*;

M – Size (cardinality) of the index set (average number of traced individuals per index case);

c – Tracing service reduction factor;

e – Vaccination efficacy (% of vaccinations that result in a "take"). To simplify the exposition we assume initially that $e = 1$. This assumption is relaxed in the analysis; and

D – Epidemic detection threshold.

3.2 Definitions and Derivations of Transitions

The infection rate is given by

$$\alpha(t) = \frac{R_0 E(I)}{S(0)},$$

(4)

where R_0 is the basic reproductive ratio, $E(I)$ is the mean duration of the infectious stage, and $S(0)$ is the size of the population at the beginning of the epidemic.

The tracing rate is

$$r_T(t) = \begin{cases} \dfrac{Min\{qV(t), cT(t)\}}{cT(t)} & \text{if } T(t) > 0 \\ 0 & \text{Otherwise} \end{cases}.$$

(5)

The tracing queue is given by the following recursive equation:

$$T(t) = T(t-1)(1 - r_T(t-1)) + MQ_1(t),$$

(6)

where $Q_1(t)$ is the number of new index cases at time t.

The number of newly named infectives in the tracing queue is given recursively by

$$L(t) = L(t-1)(1 - r_T(t-1)) + \omega_0(A^0(t) + B^0(t)),$$

(7)

The sum $A^0(t) + B^0(t)$ is the total number of PT infectives at time t.

The vaccination rate in the general queue is,

$$r_G(t) = Min\left\{1, \frac{V(t) - cT(t)r_T(t)}{S(t) + A^-(t) + A^+(t) + B^-(t) + B^+(t) + (1 - \omega_0)(A^0(t) + B^0(t))}\right\}.$$

(8)

11

Note that the general queue may include individuals that are susceptible, non-*PT* (both immunable and non-immunable), and *PT* not newly named.

Let,

$$\omega(t) = \frac{L(t)}{T(t)}.$$ (9)

$\omega(t)$ is the estimated fraction of the tracing capacity that is applied to newly named *PT* infectives. It can be seen that (9) is a natural generalization of (2) for the tracing queue. The remaining portion $1 - \omega(t)$ of the tracing capacity generates the *residual trace vaccination rate*, which is applied proportionally to individuals that are not newly named infectives. Thus,

$$r^+(t) = \frac{(1 - \omega(t))T(t)r_T(t)}{S(t) + A^-(t) + A^+(t) + B^-(t) + B^+(t) + (1 - \omega_0)(A^0(t) + B^0(t))}.$$ (10)

The vaccination rates are non-zero only after the epidemic is detected. Detection occurs only after D symptomatic individuals report to emergency rooms. D is the *epidemic detection threshold,* which indicates the alertness and responsiveness of the medical and public health system.

The hazard functions of the various stages are:

$$\varphi_X(j) = \frac{P_X(j)}{1 - \sum_{k=0}^{j-1} P_X(k)}, \quad X = A, B, I, Q.$$ (11)

The rate at which pre-*PT* infectives become *PT* depends on the rate at which infectious individual become index cases.

Let

$$\beta_j^l = \frac{P_I(j+l)}{1-\sum_{k=0}^{j} P_I(k)}, \quad l=1,2,\dots \tag{12}$$

β_j^l is the probability that an infectious individual, who is currently at the j-th day of his/her infectious period (I), will be detected l days from now. Notice that if $l=1$, then $\beta_j^l = \varphi_B(j)$.

Based on our assumption of homogeneous free mixing, the probability $u_l(t)$ that an individual who got infected on day t will become PT on day $t+l$ is,

$$u_l(t) = \frac{\sum_{k=1}^{\infty} \beta_k^l I_k(t)}{\sum_{k=1}^{\infty} I_k(t)}. \tag{13}$$

Thus, the probability $w_j(t)$ that a pre-PT infective who is at the j-th day of the incubation period at day t, will become PT at $t+1$ is,

$$w_j(t) = \frac{u_{j+1}(t-j)}{1-\sum_{l=1}^{j} u_l(t-j)}. \tag{14}$$

3.3 The Difference Equations

The following set of difference equations describes the epidemic progression in case of intervention:

$$S(t+1) = S(t)[1-\alpha(t)I(t)][1-r_G(t)-r^+(t)] \tag{15}$$

$$A_1^-(t+1) = [\alpha(t)S(t)I(t)][1-r_G(t)-r^+(t)](1-u_1(t)) \tag{16}$$

13

$$A_1^0(t+1) = [\alpha(t)S(t)I(t)][1-r_G(t)-r^+(t)]u_1(t) \tag{17}$$

$$A_{j+1}^-(t+1) = A_j^-(t)[1-r_G(t)-r^+(t)](1-\varphi_A(j))(1-w_j(t)) \tag{18}$$

$$A_{j+1}^0(t+1) = A_j^-(t)[1-r_G(t)-r^+(t)](1-\varphi_A(j))w_j(t) \tag{19}$$

$$\begin{aligned} A_{j+1}^+(t+1) &= (A_j^+(t)(1-r_G(t)+r^+(t)) \\ &\quad + A_j^0(t)(1-\omega_0 r_T(t)-(1-\omega_0)(r_G(t)+r^+(t))))(1-\varphi_A(j)) \end{aligned} \tag{20}$$

$$B_{j+1}^-(t+1) = (B_j^-(t)(1-\varphi_B(j))+A_j^-(t)\varphi_A(j))(1-r_G(t)-r^+(t))(1-w_j(t)) \tag{21}$$

$$B_{j+1}^0(t+1) = (B_j^-(t)(1-\varphi_B(j))+A_j^-(t)\varphi_A(j))(1-r_G(t)-r^+(t))w_j(t) \tag{22}$$

$$\begin{aligned} B_{j+1}^+(t+1) &= (B_j^+(t)(1-\varphi_B(j))+A_j^+(t)\varphi_A(j))(1-r_G(t)-r^+(t))+ \\ &\quad +(B_j^0(t)(1-\varphi_B(j))+A_j^0(t)\varphi_A(j))(1-\omega_0 r_T(t)-(1-\omega_0)(r_G(t)+r^+(t))) \end{aligned} \tag{23}$$

$$\begin{aligned} B_{j+1}^*(t+1) &= ((A_j^-(t)+A_j^+(t))(1-r_G(t)-r^+(t))+ \\ &\quad + A_j^0(t)(1-\omega_0 r_T(t)-(1-\omega_0)(r_G(t)+r^+(t))))\varphi_A(j)+B_j^*(t)(1-\varphi_B(j)) \end{aligned} \tag{24}$$

$$I_1(t+1) = \sum_{j=1}^{\infty} B_j^*(t)\varphi_B(j) \tag{25}$$

$$I_{j+1}(t+1) = I_j(t)(1-\varphi_I(j)) \tag{26}$$

$$Q_1(t+1) = \sum_{j=1}^{\infty} I_j(t)\varphi_I(j) \tag{27}$$

$$Q_{j+1}(t+1) = Q_j(t)(1-\varphi_Q(j)) \tag{28}$$

Explanation of the Equations

First we observe that the vaccination rates are as follows: a fraction ω_0 of the PT infectives—the newly named infectives—are vaccinated at a rate $r_t(t)$, while the rest of the population is vaccinated at a rate $r_G(t) + r^+(t)$. Recall that the parameter $r^+(t)$ is the residual portion $1-\omega(t)$ of the trace vaccination capacity that is applied to ("wasted" on) individuals that are not newly named PT infectives.

Equation (15): The remaining susceptibles are those who have not been vaccinated nor infected.

14

Equations (16), (17): The newly infected are among those who have not been vaccinated neither in the general queue nor by the residual tracing capacity. The parameter $u_1(t)$ is the probability that a newly infected becomes immediately *PT*.

Equation (18): The immunable pre-*PT* infectives are those who have not been vaccinated (neither in the general queue nor by the residual tracing capacity), are still immunable $(1 - \varphi_A(j))$ and have not become *PT* $(1 - w_j(t))$.

Equation (19): The immunable *PT* infectives at time $t+1$ comprise immunable pre-*PT* infectives ($A_j^-(t)$) who have not been vaccinated, are still immunable $(1 - \varphi_A(j))$, and have become *PT* $(w_j(t))$.

Equation (20): The immunable post-*PT* infectives at time $t+1$ comprise previously immunable *PT* ($A_j^0(t)$) and post-*PT* ($A_j^+(t)$) infectives that have not been vaccinated and remain immunable $(1 - \varphi_A(j))$. The vaccination rate of the *PT* individuals is a convex combination of the (net) tracing rate and the combined vaccination rate of the general queue and the residual tracing capacity.

Equations (21)-(23): These equations are similar to (18)-(20). They represent the transition from an immunable stage to a non-immunable stage.

Equations (24): This equation records the total number of the non-immunable infectives. We need the two representations of stage *B* cohort ((21)-(23) and (24)) because of the fact that vaccinating individuals at that stage is ineffective; they will eventually become sick. Thus, (21)-(23) are needed for determining the vaccination queue sizes for pre-*PT*, *PT*, and post-*PT* infectives, while (24) counts the individuals who will eventually become infectious (see Equation (25)).

Equation (25): The newly infectious individuals comprise infectives whose incubation period has ended.

Equation (26): The remaining infectious individuals at stage I are those who have not been detected yet.

Equation (27): The newly isolated infectious individuals (new index cases) are those who have been detected.

Equation (28): The remaining individuals in isolation are those who have not been removed yet (recovery or death).

The model that has been described above is general and can represent several vaccination policies. Specifically, once the vaccination process has been initiated, the *MVP* implies that $r_T(t) = r^+(t) = \omega_0 = 0$ for all t, and $r_G(t) > 0$ for all t, such that $S(t) > 0$. In *TVP*, $r_G(t) = 0$ for all t, and $r_T(t), r^+(t) > 0$ for all t, such that $T(t) > 0$.

The *PVP* policy is a combination of mass vaccination and trace vaccination where at all times treating the tracing queue preempts the general queue. Whenever there are new index cases, an appropriate vaccination capacity is allocated for tracing and vaccinating the generated named contacts (*Index Set*). The tracing/vaccination capacity allocated to the tracing queue is limited only by the total existing vaccination capacity, that is, $q = 1$. Mass vaccination is carried on with the remaining vaccination capacity. The parameter c, the tracing service reduction factor, quantifies the inefficiencies that result from the tracing process.

4. Analysis

The model developed in Section 3 is applied now to evaluate the effectiveness of the *prioritized vaccination process* (*PVP*) in comparison with the *mass vaccination process* (*MVP*) and the *trace vaccination process* (*TVP*). Recall that in *PVP* the first priority is for the tracing queue, and the remaining vaccination capacity is applied to the general queue. An individual is treated in the general queue only if he is not claimed by the tracing queue.

4.1 Base Case

Whenever it is relevant, the parameters chosen for the base case are similar to those in [4]. We also assume for this case that the values of the parameters remain constant throughout the duration of the epidemic. In particular, there are no special initial conditions. The values of the various epidemic, population, and operational parameters are shown in Table 4.1. Table 4.2 presents the characteristics of the probability mass functions of the time parameters. These probability distributions are consistent with the assumptions in [4] and the data in [8].

Value	Definition	Symbol
500,000*	Daily vaccination capacity	$V(t)$
10^{-7}	Infection rate	$\alpha(t)$
1,000	Number of initially infected	$A_1^-(0)$
10^7	Size of population	$S(0)$
4	Tracing service reduction factor	c
50	Size of the index set	M
0.7	Probability of naming a PT infective	ω_0
20	Epidemic detection threshold	D
0.975	Vaccination efficacy	E

* In [4] the vaccination capacity is assumed to be 10^6. We believe that 500,000 is a more realistic estimate, at least for Israel.

Table 4.1: *The Base Case Parameters*

Time Period	$P_{0.05}$	$P_{0.95}$	Mean	Median
Incubation (A)	1	5	3	3
Incubation (B)*	8	14	11.5	11.5
Infectious (I)	1	5	3	3
Isolation (Q)	9	15	12	12

* Time is measured from the day of infection.

Table 4.2: *The Base Case Probability Distributions.*

The probability distributions in Table 4.2 are also consistent with the limited data regarding the probable durations of the various stages that are reported mainly in [16] and [17].

The results corresponding to the base case are summarized in Table 4.3:

Vaccination Policy	Number Infected*	Duration of Epidemic	Maximum Daily Isolation Capacity Needed
PVP	1,015	57 days	1,002 beds
MVP	2,232	58 days	1,765 beds
TVP	> 108,000	> 1 year	9,380 beds

* Excluding the initially infected (1,000).

Table 4.3: *Results for the Base Case.*

If we take the exact same parameters as in [4], that is, $V(t) = 10^6$ and $\omega_0 = 0.5$, then the numbers of infected are 560 and 818 for *PVP* and *MVP*, respectively.

Figure 4.1 depicts the progression of the epidemic under each one of the three vaccination policies. The graphs indicate the number of newly infected.
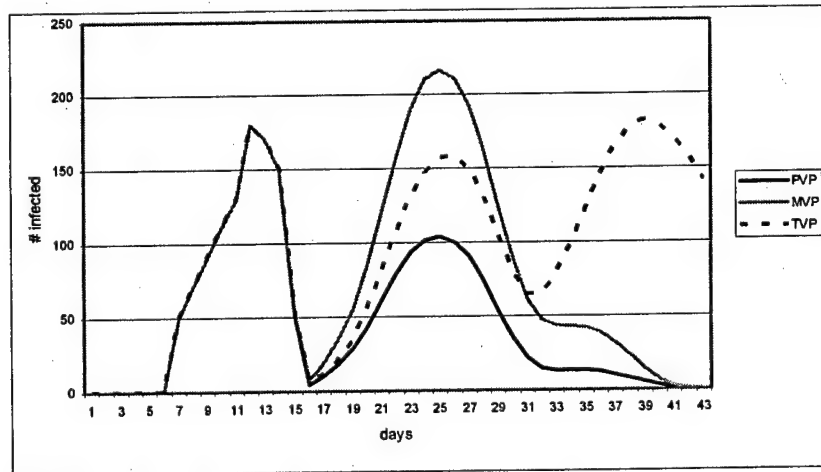
Note: Including the initially infected that are depicted in the graph of days 6-16.

Figure 4.1: *The Epidemic Progression.*

Figure 4.1 demonstrates the significant differences among the three vaccination policies: *MVP* results in a relatively large number of second-wave infected individuals, but the epidemic is eradicated much faster than when *TVP* is executed. In *TVP*, the epidemic has initially smaller peaks than in *MVP*, but it is expanding gradually over a longer period of time (in the base case, the epidemic reaches its peak on day 159). In

18

PVP, the epidemic has smaller peaks than in *TVP* and its duration is about the same as in *MVP*.

Discussion

The *PVP* is clearly more effective than the two other vaccination policies in the base case. It results in over 50% less derived infections (second wave and later infections that result from the initial attack of 1,000 infected) compared to *MVP*, and over 99% less derived infections compared to *TVP*. In both *PVP* and *MVP*, the epidemic is eradicated (and the entire population is inoculated) after almost two months. In the *TVP* case, the epidemic lasts a little over one year. The peak isolation/quarantine capacity needed for the *PVP* is less than 60% the peak capacity needed for M*VP*. The extra capacity needed in the *MVP* case is required relatively early in the epidemic since the first waves of infection may not be captured by the untargeted homogeneous vaccination process. In *TVP* and *PVP*, the vaccination is targeted at high-risk susceptibles, and therefore more stage-*A* individuals may be located and vaccinated at the early stages of the epidemic. However, the lack of massive vaccination in *TVP* results in prolonging and expanding the epidemic and thus increasing the total number infected. The peak isolation capacity in the *TVP* case (9,380) is needed on days 165 and 166 of the epidemic. These results are consistent with the conclusions in Kaplan *et al.* that *MVP* is significantly more effective than *TVP*.

Note that the relative high efficiency of *PVP* is due to the synergy that is created by combining mass and trace vaccination. Mass vaccination builds up herd immunity that effectively reduces the value of R_0, thus amplifying the effect of the tracing part of the process (See Figure 3 in [4]).

In the absence of effective disease detection systems that can indicate the occurrence of a bio-attack event, the infected individuals in the first wave of infection—those who were infected by the initial bio-attack—cannot be helped. That is why the three graphs in Figure 4.1 coincide during days 1-16.

4.2 Sensitivity Analyses

Is the evident dominance of *PVP* over *MVP* and *TVP* robust? Does it dominate for other sets of parameters?

To address these questions we perform sensitivity analysis with respect to some key parameters. Since in most cases *TVP* turns out to be inferior to *PVP* and *MVP* by almost two orders of magnitude, the comparisons in the following will focus at *MVP* and *PVP* only. The number of infectives shown in the analysis excludes those who were initially infected by the bioattack ($A_1^-(0)$).

Tracing Service Reduction Factor – *c*

In the base case, we assumed that the tracing process consumes four times the vaccination resources needed for mass vaccination, that is, $c = 4$. This value is adopted from [4]. Arguably, the larger the value of *c*, the lower the relative efficiency of the tracing process, and thus the less likely it is that *PVP* will outperform *MVP*. Figure 4.2 presents the effect of increasing *c* in increments of 10 on the effectiveness of *PVP*. Obviously, the varying of *c* does not affect the *MVP*, since there is no tracing activity. For *PVP*, the number of infected increases from 990 ($c = 1$). The break-even value of the *tracing service Reduction Factor* for *PVP* compared to *MVP* is $c = 65$. In other words, the tracing service rate must be more than 65 times slower than the general vaccination rate to render *MVP* more effective.
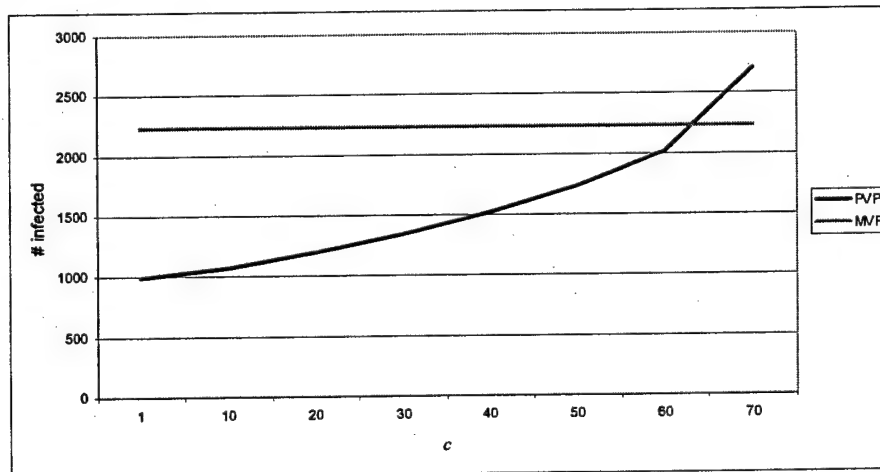

Figure 4.2: *Number of Infected as a Function of the Tracing Service Reduction Factor.*

Size of the Index Set – *M*

Similarly to the *tracing service reduction factor c*, the average number of cases that are traced per index case *M* does not affect *MVP*. However, increasing *M*, without increasing the value of ω_0 at the same time, will clearly have a negative effect on *PVP* (and *TVP*) because of the inefficiencies that result from the tracing service reduction factor. Figure 4.3 presents the effect of varying *M* between 50 (the base case) and 500 on the performance of *PVP*. Notice that the effect is relatively small in this range. Increasing *M* by an order of magnitude results in less than 35% more infectives.
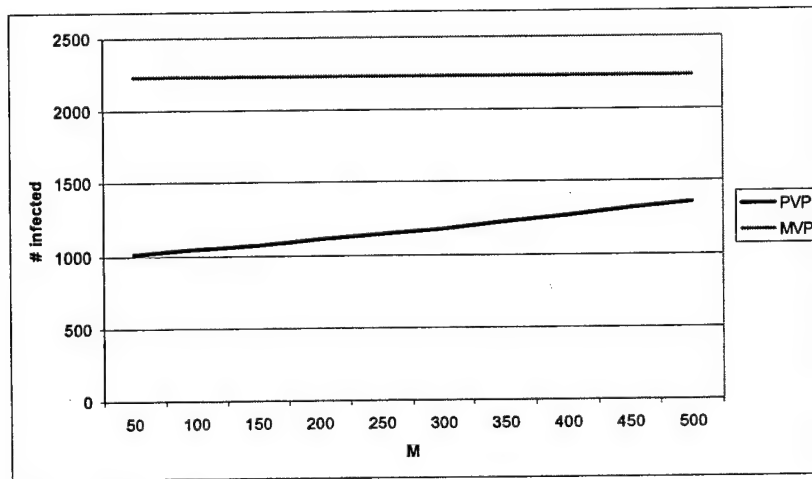
Figure 4.3: *Number of Infected in PVP as a Function of the Size of the Index Set.*

Epidemic Detection Threshold – *D*

One would expect that the effectiveness of the response process will depend on the situational awareness of the healthcare system. The faster the outbreak of the epidemic is detected, the earlier response actions can be taken, and therefore fewer infected cases would be expected. Figure 4.4 shows the effect of the epidemic detection threshold on *PVP* and *MVP*. The effect of varying the detection threshold in the *PVP* case is similar to the effect in the *MVP* case: Moving from $D = 100$ to a fully alert system ($D = 1$) results in 33% less infectives in both cases.
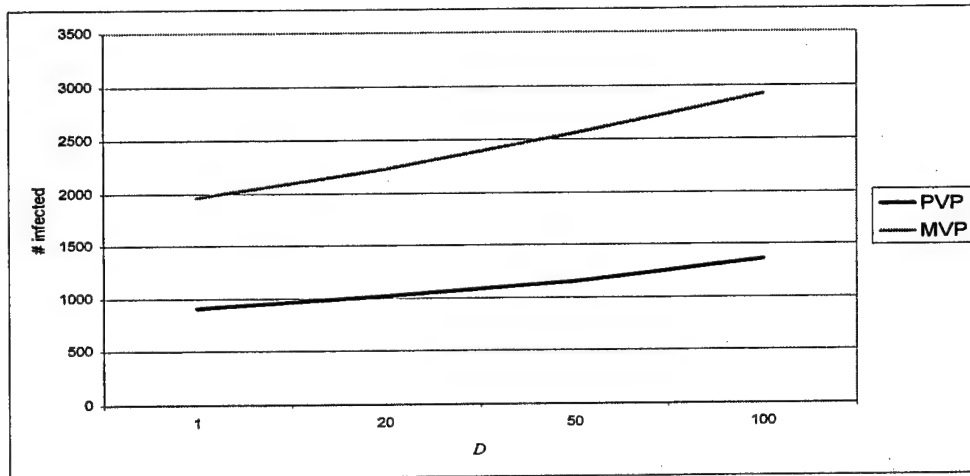
Figure 4.4: *Number of Infected as a Function of the Detection Threshold.*

Daily Nominal Vaccination Capacity – V

The results are sensitive to the assumption regarding the effective daily vaccination capacity, which is assumed here to be fixed over time. Figure 4.5 presents the effect of varying the values of V.
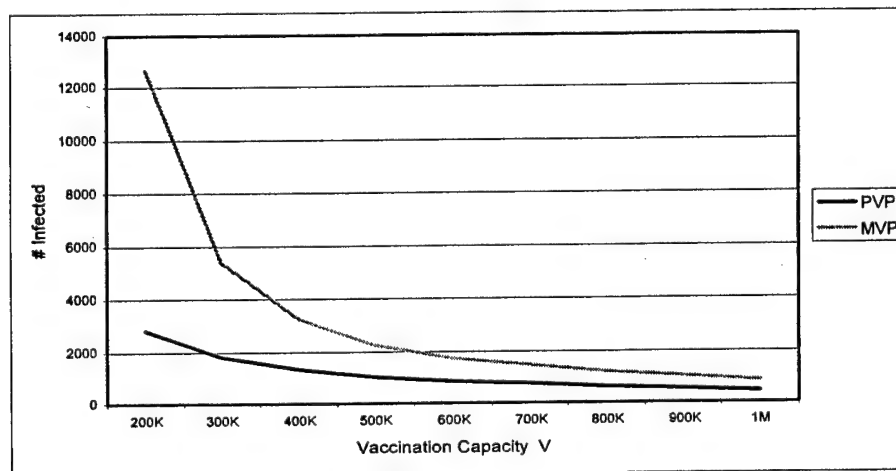

Figure 4.5: *Number of Infected as a Function of the Vaccination Capacity.*

Clearly, the effectiveness of *MVP* is more sensitive to the value of V than *PVP*. The advantage of *PVP* over *MVP* is most notable for small values of V. When the vaccination capacity is only 100,000 a day (not shown in the graph), the number of infected in the *MVP* case is more than 14 times higher than that number in the *PVP* case. This advantage

declines as V increases since the relative impact of the tracing process gets smaller. If $V = 1M$, then *PVP* results in 45% fewer casualties compared to *MVP*.

Tracing Effectiveness – ω_0

This parameter reflects the efficiency of the tracing process. It is the maximum possible probability to trace an infective. In the base case, we assumed that this efficiency cannot exceed 70%. Clearly, the lower the upper bound, the less advantageous are *PVP* and *TVP* compared to *MVP*. Figure 4.6 shows the effect of ω_0 on the number of infectives. *TVP* is more effective than *MVP* if $\omega_0 \geq 0.99$, that is, only in the case of extremely high tracing effectiveness. For $\omega_0 \geq 0.1$, *PVP* is the most effective policy. Its advantage over *MVP* increases, as ω_0 gets larger. If $\omega_0 = 0.5$, then *PVP* results in 39% fewer infectives compared to *MVP*. If $\omega_0 = 0.9$, then the number of infectives is 70% lower.
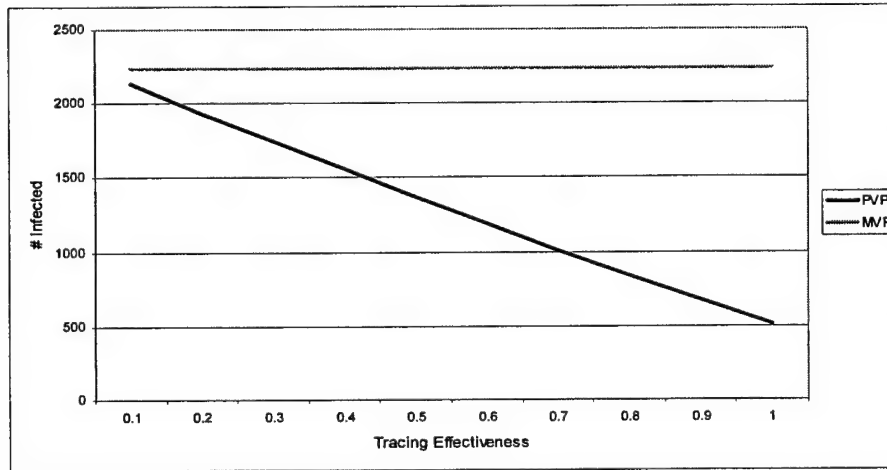

Figure 4.6: *Number of Infected as a Function of ω_0.*

Effect of Initial Conditions

During the initial stages of the epidemic some of the parameters may have different values than later on in the epidemic. We consider here three such parameters: the daily vaccination capacity V, the infection rate α, and the distribution function of the duration of the infectious period $P_I(j)$. Due to set-up time, we assume that during the first day of

vaccination $V(1) = 200,000$ only, compared to $V(t) = 500,000$ $t > 1$. In the base case, $\alpha = 10^{-7}$, which implies that $R_0 = 3$. During the first wave of infection, when the epidemic has not been detected yet, one may expect a higher infection rate. Thus, we assume that during the first wave $R_0 = 4$. The lack of situational awareness leads also to an extended stage I period during the first wave. Therefore, we assume that the mean time of stage I during the first wave is $E(I) = 4$ days, compared to three days during the rest of the epidemic period. Table 4.4 presents the effect of these initial conditions on the number of infected—in comparison to the base case.

Scenario	PVP	MVP
Base Case	1,015	2,232
Initial Conditions	2,131	4,218
Base Case & $E(I) = 4$	1,814	3,548
Base Case & $R_0 = 4$	1,052	2,415
Base Case & $V(1) = 200K$	1,083	3,415

Table 4.4: *The Effect of Initial Conditions.*

The effect of the initial conditions is not negligible. They result in almost 90% more casualties in *MVP* and twice that number in *PVP*. It is also observed that the length of the infectious period (Stage *I*) distribution function has the largest single impact among the three factors that affect the initial conditions. It follows that early pre-symptomatic detection of the epidemic is crucial in any vaccination policy.

5. Summary and Conclusions

We have developed a new difference-equation model that captures key epidemiological and operational features of a bioattack response process. The model represents several inter-temporal parameters and processes—in particular, the process in which infected individuals become potentially traceable. The model has been implemented to analyze three vaccination policies: the *mass vaccination process* (*MVP*), the *trace vaccination process* (*TVP*), and the newly suggested *prioritized vaccination process* (*PVP*), in which high-priority tracing is conducted in conjunction with a complement mass vaccination effort.

The first conclusion of the analysis is a confirmation of the general result in [4] and [5], that is, mass vaccination is far more effective than trace vaccination. The second conclusion is that the prioritized vaccination policy is superior to the mass vaccination policy for any set of realistic parameters. Moreover, since the *PVP* "wastes" vaccination resources on tracing, one may argue that the tradeoff between *MVP* and *PVP* may be sensitive to the assumption regarding the service tracing service reduction factor (c) that reflects the degradation in the vaccination rate due to tracing. It is shown that this is not the case; *PVP* is more effective than *MVP* even if this ratio is higher than 60. It is also noted that the advantage of *PVP* over *MVP* increases as the vaccination resources become more limited (see Figure 4.5). The effectiveness of the *PVP* is also relatively insensitive to the size of the index set *M*. Tracing as low as five individuals per index case may be sufficient for obtaining satisfactory results. Finally, it is noted that initial awareness to such an attack, which may reduce the length of the first generation infectious stage (*I*), can have a significant effect on the total number of infected individuals. From the logistical point of view, the maximum daily isolation capacity that is needed for *MVP* is considerably higher than the capacity needed for *PVP*.

Recall that the model presented here assumes homogeneous mixing. This assumption may not be realistic in many possible scenarios. Future work in response-policy analysis must take into account spatial and social effects. The newly emerging concept of "small world" network [18] may be utilized to model these effects.

REFERENCES

[1] Huerta, M., Balicer, R.D., and Leventhal, A., "SWOT Analysis: Strengths, Weaknesses, Opportunities and Threats of the Israeli Smallpox Revaccination Program," *Israel Medical Association Journal*, 5 (2003), pp. 42-46.

[2] Broad, W.J., "Study Uses Math Model to Determine Effects of a Smallpox Attack," *New York Times*, July 8, 2002.

[3] Healy, B., "Time for Pause," *US News & World Report*, April 21, 2003.

[4] Kaplan, E.H., Craft, D.L., and Wein, L.M., "Emergency Response to a Smallpox Attack: The Case for Mass Vaccination," *Proceedings of the National Academy of Science*, 99 (16) (2002), pp. 10935-10940.

[5] Kaplan, E.H., Craft, D.L., and Wein, L.M., "Analyzing bioterror response logistics: the case of smallpox," *Mathematical Biosciences*, 183 (2003), pp. 33-72.

[6] Halloran, M.E., Longini, Jr., I.M., Azhar, N., and Yang, Y., "Containing Bioterrorist Smallpox", *Science*, 298 (2002), 1428-1432.

[7] Kaplan, E.H., Wein, L.M.; Halloran, M.E., Longini, I.M., "Smallpox Bioterror Response," Letter to the Editor, *Science*, 300 (2003), pp. 1503-1504.

[8] Meltzer, M.I., Damon, I., LeDuc, J.W., and Millar, J.D., "Modeling Potential Responses to Smallpox as a Bioterrorist Weapon," *Emerging Infectious Diseases*, 7 (6) (2001), pp. 959-969.

[9] Koopman, J., "Controlling Smallpox," *Science* 298 (2002), pp. 1342-1344.

[10] Müller, J., Kretzschmar, M., and Dietz, K., "Contact Tracing in Stochastic and Deterministic Epidemic Model," *Mathematical Biosciences*, 164 (2000), pp. 39-64.

[11] Newman, M.E.J., "Spread of Epidemic Disease on Networks," *Physical Review*, E 66 (2002), pp. 0161281-01612811.

[12] Müller, J., Schönfisch, B., and Kirkilionis, M., "Ring Vaccination," *J. Mathematical Biology*, 41 (2000), pp. 143-171.

[13] Rhodes, C.J., and Anderson, R.M., "Epidemic Threshold and Vaccination in a Lattice Model of Disease Spread," *Theoretical Population Biology*, 52 (1997), pp. 101-118.

[14] Epstein, J.M., Cummings, D.A.T., Chakravarty, S., Singa, R.M., and Burke, D.S., "Toward a Containment Strategy for Smallpox Bioterror: An Individual-Based Computational Approach," Brookings Institution – Johns Hopkins University Center on Social and Economic Dynamics, Working Paper No. 31 (2002).

[15] Bozzette, S.A., Boer, R., Bhatnagar, V., Brower, J.L., Keeler, E.B., Morton, S.C., and Stoto, M.A., "A Model for a Smallpox-Vaccination Policy," *The New England Journal of Medicine*, 348 (5) (2003), pp. 416-425.

[16] Fenner, F., Henderson, D.A., Arita I., Jexek, Z., and Lanyi, I.D., "Smallpox and its Eradication," World Health Organization (WHO), Geneva, (1988).

[17] Singh, S., "Some Aspects of the Epidemiology of Smallpox in Nepal," World Health Organization (WHO), SE/69.10, Geneva (1969).

[18] Watts, D.J., and Strogatz, S.H., "Collective Dynamics of 'Small World' Networks," *Nature*, 393 (4) (June 1998), pp. 440-442.

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